

## REMARKS

Claims 1, 3-5, 7, 11, 13, 17-19, 29, 37, 40-42, 46, 56-58, 60-63, and 67-72, as amended, are pending in this application for the Examiner's review and consideration. Independent claims 1, 37 and 60 have been amended to recite that a single active agent of testosterone is present in the formulation, while also reciting the presence of water. Independent claims 1, 37 and 60 have also been amended to recite that the propylene glycol and permeation enhancer are present in a weight ratio of 2:1 to 1:1, and the total amount of polyalcohol and permeation enhancer is not more than 15% of the formulation, as previously recited in claim 6, a claim that has been canceled. Claim 60 was amended to consist of the specific components of the formulation and delivery vehicle as set forth in the dependent claims. Claims 7, 46 and 67 and others have been amended to avoid inconsistencies or redundancy over the independent claims. As no new matter is introduced by any of these changes, they should all be entered at this time at least to reduce the issues for appeal by eliminating the formality rejections.

Claims 7 and 46 were objected to and claim 67 was rejected as being indefinite. The amendments made herein now overcome these objections and rejection such that they should be withdrawn. As noted above, other dependent claims have been reviewed and amended to conform to the amendments made to the independent claims.

Claims 1, 3-8, 10, 11, 13, 15, 20, 22, 37, 40-43, 45-47, 56, 57, 60-62 and 68 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over International Patent Application Publication No. WO 02/22132 to Gray et al. (US Patent No. 7,030,104 is the English-language equivalent and relied upon by the Office Action, referred to hereinafter as "Gray") in view of US Patent No. 6,503,894 to Dudley et al. (referred to hereafter as "Dudley"), and an article by Wang et al. (the Journal of Clinical Endocrinology and Metabolism, 2000, referred to hereinafter as "Wang"). Applicants respectfully disagree.

As previously explained, Gray relates to a topical hormonal composition comprising as active ingredients, a progestogen derived from 19-nor progesterone and estradiol or one of its derivatives, a vehicle which allows the systemic passage of said active ingredients, chosen from the group constituted by a solubilizing agent, an absorption promoting agent, a film-forming agent, a gelling agent and their mixtures, in combination or in a mixture with suitable excipients for the realization of a gelled and/or film-forming pharmaceutical form.

In contrast, the present claims as amended are now specifically directed to a formulation containing testosterone as the active agent, or method of use thereof, or a kit containing such a formulation. Therefore, as acknowledged in the office action, Gray does not teach each and every element of the present claims, and the Dudley and Wang references are cited.

Dudley relates to a pharmaceutical composition useful for treating hypogonadism comprising an androgenic or anabolic steroid, a C1-C4 alcohol, a penetration enhancer such as isopropyl myristate, and water.

Wang discloses packaging hydroalcoholic gels containing 1 wt.% testosterone in a multidose bottle with an actuator pump for treatment of hypogonadal males.

First of all, there is no teaching or suggestion in either reference to motivate a person of ordinary skill in the art to replace the active agents in the composition of Gray, i.e., progestogen derived from 19-nor progesterone and estradiol or one of its derivatives, with an androgenic or anabolic steroid disclosed in Dudley. Importantly, Gray is specific for cutaneous topical preparations containing a synthetic progestogen and a natural or synthetic estrogen. Therefore, a person of ordinary skill in the art, following the teachings of Gray, will not choose to replace its active agents with testosterone mentioned by Dudley.

The final office action disagrees with this statement and instead suggests on page 6 that it would well be within the purview of a skilled artisan to use testosterone in the formulations of Gray. Assuming, *arguendo*, that this substitution would be considered by a skilled artisan, it then becomes necessary to consider in which of the numerous formulations of Gray would testosterone be substituted in place of the active agents taught by Gray.

The final office action cites a portion of Table I of Gray, but conveniently leaves out more than half of that table. While formulations G29-287, G29-299 and Tx11323 batch 12 have similar solvents to what are used in the presently claimed formulations, there is no disclosure even in those examples of any relationships or amounts for those components to arrive at what is presently claimed. The formulations that were omitted from the office action reproduction of Table I, however, do not include the recited components or amounts that are set forth in the present claims. In addition, Applicants recite a preferred ratio for the polyalcohol and permeation enhancer (i.e., the monoalkyl ether of diethylene glycol) of from 2:1 to 1:1. Although using a different permeation enhancer, three of the omitted formulations teach a ratio of 2.67:1 (i.e., 8:3), a ratio that is outside of the presently claimed range. The testing of those

formulations leads Gray to conclude in column 12, lines 43-56 that when norgestrel acetate is combined with estradiol, a promoter effect of estradiol on the diffusion of norgestrel acetate was found using two pairs of different solvents: the propylene-glycol/Transcutol pair (Table 3) and the propylene glycol/Solketal pair (Table 4). This teaches a skilled artisan that either formulation is suitable for obtaining the promoter effect.

Gray then presents in vivo and in vitro test results in Column 13 and concludes that to ensure a complete therapeutic effect in all women it would be worthwhile to obtain higher circulating levels of norgestrel acetate and that the results of diffusion in vitro were improved by other formulations (see col. 13, lines 40-45). He then prepares a new series of gels based on the formulation of Table 7, which does not include a permeation enhancer of a monoalkyl ether of diethylene glycol and which has a ratio of propylene glycol to permeation enhancer (i.e., absorption promoter) of 2.67:1 (8:3). As discussed by Gray in col. 16, lines 20 to 56, the best results were found with formulations G9-100, G49-106, G49-108 and G42-120. The absorption promoters (or permeation enhancers) used for those formulations are octanoic acid, octadec-9-enoic acid, dodecanoic acid and solketal (i.e., (2,2-dimethyl-1,3-dioxolan-4-yl)methanol), respectively.

Gray furthermore observed that the first three formulations contain absorption promoters that are "badly tolerated" by the skin such that those formulations "must be used with caution" (column 16, lines 29-30). Based on that he concludes that formulation G42-120 is the most preferred.

Accordingly, it is respectfully submitted that a skilled artisan, following the reasoning in the final office action, would not be led to the formulations of Table 1, but instead would be taught to substitute testosterone into the G42-120 formulation which provided the best performance and safety. As noted above, this formulation does not use a permeation enhancer of a monoalkyl ether of diethylene glycol and does not include a ratio of propylene glycol to permeation enhancer of 2:1 to 1:1. The other three formulations that provided the best results are also not covered by the present claims as the fatty acids are specifically excluded by the present claims in order to avoid undesirable odor and irritation from such compounds during use of the formulation. Thus, a fair reading of the entire Gray reference would not lead to a formulation according to the present claims.

And in addition, a skilled artisan would have no expectation of success to replace progesterone and estradiol taught in Gray with testosterone disclosed in Dudley. These are different active agents that perform differently even if used with similar solvents. As supported by a previously submitted research paper (P. Karande et al., *High Throughput Screening of Transdermal Formulations*, Pharmaceutical Research, vol. 19, no. 5, May 2002, pp. 655-660), more than 200 chemical enhancers including surfactants, fatty acids, fatty alcohols, and organic solvents have been used in attempts to increase transdermal drug transport and generally testing is needed to determine which are the most suitable for a particular active.

Another difference over Gray is that Gray's disclosure is clearly directed at combinations of actives where one is used to favor the diffusion of one of the actives over the other. In contrast, the present claims are directed to a single active, testosterone.

The combination of Gray and Dudley fails to obtain the present claims for additional reason. Ignoring the fact that Dudley does not specifically disclose, teach or even mention that testosterone could or should be substituted for progesterone derived from 19-nor progesterone and estradiol or one of its derivatives, Dudley also prefers to use solvents that are not covered by or obvious variations of those that are recited in the present claims. Dudley prefers to use fatty acid derivatives, and in particular, isopropyl myristate, for his testosterone formulations (see the AndroGel® formulation in Table 5 of Dudley). Even though Dudley does mention other compounds such as diethylene glycol monomethyl ether in his listing of permeation enhancers, he attributes no preference to that compound. Thus, one of ordinary skill in the art, reading Dudley, will not be taught or motivated to select diethylene glycol monomethyl ether as taught in Gray in place of isopropyl myristate as the transdermal enhancer for the active agent testosterone as presently claimed. And as Gray does not prefer diethylene glycol monoethyl ether as an absorption agent, there is no motivation to use that enhancer from Dudley as he does not even mention it in his listing of useful permeation enhancers. Thus, claims 7, 42, 60-63 and 68-72 are further distinguishable from the cited references.

Accordingly, the compositions of Gray and Dudley cannot be combined as suggested in the office action except by relying on the disclosure of the present application and performing a hindsight analysis of the claims. The determination of obviousness is not whether a person could, with full knowledge of the present invention, reproduce it from prior art. The question is whether there would be some teaching, suggestion, or motivation in the art to do so. This

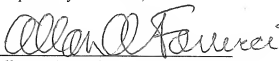
judgment cannot be made with the benefit of hindsight and Applicants submit that it is improper to take isolated disclosures from other formulations and change them in light of the now-known template of the present application, unless there is some direction in the prior art that would suggest this or that would clearly motivate a skilled artisan to do so. As no such motivation, teaching or suggestion exists in the cited references, the presently claimed invention is not obvious in view of Gray and Dudley along with Wang. In fact, Wang apparently is cited for his disclosure of a container, but this does not modify the formulations of Gray or Dudley to arrive at Applicants' claims.

In view of the foregoing, as the cited references do not render the present claims obvious, and the obviousness rejection should be withdrawn. Accordingly, it is believed that the entire application is now in condition for allowance, early notice of which would be appreciated.

Date:

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Respectfully submitted,



Allan A. Fanucci (Reg. No. 30,256)

**WINSTON & STRAWN LLP**  
CUSTOMER NO. 28765  
(212) 294-3311